SUMMARY OF PRODUCT CHARACTERISTICS

BRUSTAN PLUS TABLET

(Ibuprofen and Paracetamol Tablet)

1. NAME OF THE MEDICINAL PRODUCT

IBUPROFEN AND PARACETAMOL TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BRUSTAN PLUS TABLET S
Each film-coated tablet contains:
Ibuprofen BP …….400 mg
Paracetamol BP……..325 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications [1]

For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

4.2 Posology and method of administration [1, 2]

For short term-use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

Adults: One tablet to be taken up to three times per day with water. Leave at least six hours between doses.

To minimise side effects, it is recommended that patients take BRUSTAN PLUS TABLETS with food.

Elderly: No special dosage modifications are required (see section 4.4).

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

Not for use by children under 18 years.

Method of Administration
For oral administration

4.3 Contraindications [1]

This product is contraindicated:

- In patients with a known hypersensitivity to ibuprofen, paracetamol or any other excipients in the product.
- In concomitant use with other paracetamol-containing products – increased risk of serious adverse effects (see section 4.5).
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see section 4.4).
- Patients with defects in coagulation.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) (see section 4.4).
- In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see section 4.5).
- During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension (see section 4.6).

4.4 Special warnings and precautions for use [1]

Do not exceed the recommended dose.

If symptoms persist consult your doctor.

Keep out of the sight and reach of children.

Paracetamol
The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Ibuprofen
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see section 4.2).

Elderly
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Caution is required in patients with certain conditions:

Respiratory disorders
In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

SLE and mixed connective tissue disease
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Cardiovascular and cerebrovascular effects
Appropriate monitoring and medical advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Reported clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, reported epidemiological studies

do not suggest that low dose ibuprofen (e.g. ≤1200mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided. Careful consideration should be exercised before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) particularly if high doses of ibuprofen (2400 mg/day) are required.

Cardiovascular, renal and hepatic impairment
The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see section 4.3).

Gastrointestinal effects
NSAIDS should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.

Dermatological effects
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility
There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may impair female fertility by an effect on ovulation and is not recommended in women attempting to conceive. This is reversible on withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

4.5 Interaction with other medicinal products and other forms of interaction [1]

BRUSTAN PLUS TABLET (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see section 4.3).

BRUSTAN PLUS TABLET (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

- *Acetylsalicylic acid:* Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor (see section 4.4).

- Reported experimental data suggest that Ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1)

- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see section 4.3).

BRUSTAN PLUS TABLET (like any other paracetamol containing products) should be used with caution in combination with:

- *Cholestyramine:* The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.

- *Metoclopramide and Domperidone:* The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

- *Warfarin:* The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

BRUSTAN PLUS TABLET (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

- *Anticoagulants:* NSAIDs may enhance the effects of anticoagulants, i.e. warfarin (see section 4.4).

- *Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics:* NSAIDs may reduce the effects of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

- *Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs):* Increased risk of gastrointestinal bleeding (see section 4.4).

- *Cardiac glycosides:* NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

- *Ciclosporin:* Increased risk of nephrotoxicity.

- *Corticosteroids:* Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

- *Lithium:* Decreased elimination of lithium.

- *Methotrexate:* Decreased elimination of methotrexate.

- *Mifepristone:* NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

- *Quinolone antibiotics:* reported animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

- *Tacrolimus:* Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

- *Zidovudine:* Increased risk of haematological toxicity with NSAIDS are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation [1]

Pregnancy

There is no experience of use of this product in humans during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Reported epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see section 4.3).

Lactation

Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines [1]

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects [1, 2]

Reported clinical trials with combination product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

The following table lists adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use.

Adverse events which have been associated with Ibuprofen alone or Paracetamol alone are given below, tabulated by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1]
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus[2]
	Very rare	In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been reported.

System Organ Class	Frequency	Adverse Event
		Severe hypersensitivity reactions. Symptoms can include facial, tongue and throat swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)[2]
Psychiatric Disorders	Very rare	Confusion, depression and hallucinations, nervousness
Nervous System Disorders	Uncommon	Headache and dizziness
	Very rare	Aseptic meningitis[3], paraesthesia, optic neuritis and somnolence
Eye Disorders	Very rare	Visual impairment
Ear and Labyrinth Disorders	Very rare	Tinnitus and vertigo
Cardiac Disorders	Very rare	Cardiac failure, angina pectoris and oedema[4]
Vascular Disorders	Very rare	Hypertension[4]
Respiratory and thoracic and mediastinal disorders	Very rare	Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm, dyspnea and wheezing[2]
Gastrointestinal Disorders	Common	Abdominal pain, vomiting, diarrhoea, nausea, dyspepsia and abdominal discomfort[5]
	Uncommon	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, haematemesis[6], mouth ulceration, exacerbation of colitis and Crohn's disease[7] gastritis, pancreatitis, flatulence and constipation
Hepatobiliary Disorders	Very rare	Abnormal liver function, hepatitis and jaundice[8]
Skin and Subcutaneous Tissue Disorders	Common	Hyperhidrosis
	Uncommon	Various skin rashes[2]
	Very rare	Bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis[2].Exfoliative dermatoses, purpura, photosensitivity
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and Urinary Disorders	Very rare	Nephrotoxicity in various forms, including tubulointerstitial nephritis, nephrotic syndrome, haematuria, proteinuria and acute and chronic renal failure[9]
General Disorders and Administration Site Conditions	Very rare	Oedema, peripheral oedema, fatigue and malaise
Investigations	Common	Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased, blood urea increased.
	Uncommon	Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinease increased, haemoglobin decreased and platelet count increased.
	Very rare	Decreased hematocrit

System Organ Class	Frequency	Adverse Event

Description of Selected Adverse Reactions

[1]Examples include agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leucopenia, neutropenia, pancytopenia and thrombocytopenia.

First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising, nose and skin bleeding.

[2]Hypersensitivity reactions have been reported. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity, e.g. asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) various skin reactions, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme).

[3]The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with Ibuprofen, with symptoms such as: stiff neck, headache, nausea, vomiting, fever or disorientation have been reported (see section 4.4).

[4]Reported clinical studies suggest that use of ibuprofen particularly at high a dose (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

[5]The adverse events reported most often are gastrointestinal in nature.

[6]Sometimes fatal, particularly in the elderly.

[7] See section 4.4.

[8]In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see section 4.9).

[9] Especially in long-term use, associated with increased serum urea and oedema.

Also includes papillary necrosis.

4.9 Overdose [1]

Paracetamol

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
b) Regularly consumes alcohol in excess of recommended amounts.
c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion. The effectiveness of the antidote declines sharply after this time.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen

In children ingestion of more than 400 mg/kg of Ibuprofen may cause symptoms. In adults the dose response effect is less clear cut.

The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity has been reported in the central nervous system, manifesting as

drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties [1]

ATC Code: M01AE51 – Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID and its efficacy has been reported in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been reported to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen was reported to reduce inflammatory pain, swellings and fever.

Reported experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid

on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX-2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Paracetamol has been reported as a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been reported in pain associated with headache, toothache and dysmenorrhoea, and fever; furthermore efficacy has been reported in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and backache.

5.2 Pharmacokinetics properties [3, 4]

Ibuprofen

Ibuprofen is reported to be rapidly absorbed following administration and reported to be rapidly distributed throughout the whole body. The reported excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reported to be reached in 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are reported after 1 to 2 hours. These times may vary with different dosage forms.

The reported half-life of ibuprofen is about 2 hours.

In limited reported studies, ibuprofen appears in the breast milk in very low concentrations.

Paracetamol

Paracetamol is reported to be readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is reported to be metabolised in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is reported to be excreted as unchanged paracetamol. The reported elimination half-life varies from about 1 to 4 hours. The reported plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually reported to be produced in very small amounts by mixed-function oxidases in the liver and which is usually reported to be detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

5.3 Preclinical safety data [1]

The toxicological safety profile of ibuprofen and paracetamol has been reported to be established in animal experiments and in humans from extensive clinical experience. There are no new additional preclinical data of relevance reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate, Maize Starch, Povidone, Purified Talc, Isopropyl Alcohol , Opadry 06G53189 Orange, Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

In well closed container, at a temperature not exceeding 30ºC, protected from moisture.

6.5 Nature and contents of container

BRUSTAN PLUS TABLET are available in 10 tablets pack and such 01 or 02 blisters are packed in a carton along with package insert.

6.6 Special precautions for disposal and other handling

No special requirement

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited, India

8. MARKETING AUTHORISATION NUMBER(S)

B4-6109

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17-Dec-2015

10. DATE OF REVISION OF THE TEXT

February 2020

REFERENCES

1. Summary of Product Characteristics of Nuromol 200mg/500mg tablets, Reckitt Benckiser Healthcare (UK) Ltd, February 2018.
2. Summary of Product Characteristics of Anadin Ultra Double Strength 400mg Capsules/ Anadin LiquiFast 400mg Capsules (Ibuprofen400mg), Pfizer Consumer Healthcare Ltd., UK, August 2019.
3. Summary of Product Characteristics of Anadin Ibuprofen 200mg Tablets, Pfizer Consumer Healthcare Ltd., UK, August 2019.
4. Summary of Product Characteristics of Anadin Paracetamol Tablets, Pfizer Consumer Healthcare Ltd., UK, October 2019.